
Over-the-Counter Sunscreens: Safety and Effectiveness Data Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Kristen Hardin at 240-402-4246.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**November 2015
OTC**

Over-the-Counter Sunscreens: Safety and Effectiveness Data Guidance for Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Tel: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**November 2015
OTC**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	PHARMACEUTICAL QUALITY/MANUFACTURING DATA.....	3
III.	SAFETY DATA NEEDED TO ESTABLISH THAT AN OTC SUNSCREEN ACTIVE INGREDIENT IS GRASE.....	3
A.	Clinical Safety Testing	5
1.	<i>Human Dermal Safety Studies</i>	<i>5</i>
a.	Human irritation and sensitization studies	5
b.	Human photosafety studies	6
2.	<i>Human Absorption Studies/Maximal Usage Trial</i>	<i>7</i>
3.	<i>Pediatric Considerations</i>	<i>8</i>
B.	Nonclinical Safety Testing.....	9
1.	<i>Carcinogenicity Studies: Dermal and Systemic.....</i>	<i>9</i>
2.	<i>Developmental and Reproductive Toxicity Studies.....</i>	<i>9</i>
3.	<i>Toxicokinetics</i>	<i>10</i>
C.	Postmarketing Safety Data.....	10
IV.	EFFECTIVENESS TESTING	11
V.	ANTICIPATED FINAL FORMULATION TESTING	12

Over-the-Counter Sunscreens: Safety and Effectiveness Data Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance addresses the Food and Drug Administration's (FDA's or Agency's) current thinking about the safety and effectiveness data needed to determine whether a nonprescription (also referred to as over-the-counter (OTC)) sunscreen active ingredient or combination of active ingredients evaluated under the Sunscreen Innovation Act (SIA) is generally recognized as safe and effective (GRASE) and not misbranded when used under specified conditions.² For brevity, references to sunscreen *active ingredients*³ in this guidance also include combinations of active ingredients unless otherwise specified.

FDA is issuing this guidance in partial implementation of the SIA. Among other things, the SIA supplemented FDA's existing regulation for adding a new active ingredient or other condition to an OTC drug monograph⁴ with new procedures and review time lines for establishing that a nonprescription sunscreen active ingredient is GRASE and not misbranded when used under the conditions specified in a final sunscreen order.⁵ A critical step in that process is FDA's review

¹ This guidance has been prepared by the Center for Drug Evaluation and Research at the Food and Drug Administration.

² 21 U.S.C. ch. 9, sub. 5, part I, enacted November 26, 2014

³ For purposes of this guidance, the term *sunscreen active ingredient* refers to an active ingredient that is intended for application to the skin of humans for purposes of absorbing, reflecting, or scattering ultraviolet radiation (see section 586(10) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)).

⁴ See 21 CFR 330.14. This regulation sets out the time and extent application procedure by which a new active ingredient or other condition (e.g., dosage form, dosage strength, or route of administration) can be considered for inclusion in the OTC drug monograph system.

⁵ See sections 586A (submission of a new request for GRASE determination), 586B (preliminary filing review, eligibility determination, and request for submission of safety and effectiveness data), and 586C (GRASE determination and issuance of proposed and final orders) of the FD&C Act.

Contains Nonbinding Recommendations
Draft — Not for Implementation

of safety and efficacy data submitted by the person requesting the GRASE determination (sponsor).⁶ If FDA determines that the active ingredient in question is GRASE and not misbranded for use in nonprescription sunscreens, it will issue a final sunscreen order setting out the conditions that sunscreen products containing the active ingredient must satisfy to be marketed without an approved new drug application (NDA).⁷ Sunscreen products that satisfy those conditions and other requirements for nonprescription drugs may be marketed immediately upon issuance of the final sunscreen order and for as long as that order remains in effect. Any future rulemaking to amend the OTC sunscreen drug monograph will include the active ingredient found GRASE in the final order.⁸

The SIA also directed FDA to issue draft guidance on the data a nonprescription sunscreen active ingredient would need to meet the safety and efficacy standard for a GRASE determination.⁹ The recommendations in this guidance will help sponsors identify and obtain the safety and effectiveness data needed to show that sunscreen active ingredients are GRASE for use in nonprescription sunscreens. Unlike the review of sunscreen *products* under the new drug approval process,¹⁰ for which premarketing testing focuses on individual product formulations, the GRASE review for active ingredients takes into account the fact that the ingredient, if found GRASE, may be included in a variety of formulations that will be marketed without product-specific review and approval.

The recommendations in this guidance are designed to ensure that FDA's GRASE determinations for OTC sunscreen active ingredients under the SIA are consistent, up to date, and appropriately reflect current scientific knowledge and patterns of nonprescription sunscreen use by consumers. The recommendations reflect FDA's scientific expertise, existing technical guidance, experience from reviewing safety and efficacy data submitted for GRASE review of sunscreen active ingredients under current OTC drug regulations, and input from and concurrence by outside scientific experts. This guidance also addresses FDA's current thinking about an approach to safety-related final formulation testing that it anticipates adopting in the future.

⁶ See section 586C of the FD&C Act. FDA will also consider other relevant public data submitted by other parties or otherwise available.

⁷ See section 586C of the FD&C Act generally for detailed procedures.

⁸ See sections 586C(e)(1)(A) (effect of final sunscreen order for sunscreen active ingredient(s) found to be GRASE) and 586C(e)(3) (future amendments of OTC sunscreen monograph to include any nonprescription sunscreen active ingredient(s) subject to an effective final sunscreen order determining it to be GRASE, and to set forth the conditions of use) of the FD&C Act.

⁹ See section 586D(a)(1)(A)(ii) of the FD&C Act. The SIA also requires FDA to issue three other draft guidances on procedural matters relating to nonprescription sunscreen active ingredients: (1) format and content of data submissions (section 586D(a)(1)(A)(i)); (2) process for withdrawing requests for a GRASE determination (section 586D(a)(1)(A)(iii)); and (3) process by which FDA will carry out section 586C(c), regarding advisory committee meetings (section 586D(a)(1)(A)(iv)).

¹⁰ This process is described in 21 CFR part 314.

Contains Nonbinding Recommendations
Draft — Not for Implementation

FDA’s specific recommendations on the data needed to support a positive GRASE determination under the SIA are detailed in sections II (pharmaceutical quality/manufacturing data), III (safety data), and IV (effectiveness data). Section V presents FDA’s current thinking on an approach to safety testing of final sunscreen formulations that it anticipates adopting in the future.

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. PHARMACEUTICAL QUALITY/MANUFACTURING DATA

FDA needs information that characterizes the identity of each sunscreen active ingredient sufficiently for FDA reviewers to determine how, if at all, the safety and efficacy studies submitted for review are relevant to the ingredient for which GRASE determination is sought.¹¹ This information is also necessary to appropriately characterize the active ingredient in the final sunscreen order. Sponsors should provide the compendial status of the ingredient, including reference to a United States Pharmacopeia — National Formulary monograph. Sponsors should also provide any known chemical and/or manufacturing characteristics of the active ingredient that may be relevant to FDA’s GRASE evaluation and to the establishment of the conditions of any resulting final order.¹² Such information should include known interactions with other sunscreen active ingredients or commonly used sunscreen vehicle components, and particle size information for micronized or nanoscale active ingredients. In addition, sponsors should describe aspects of formulation, if any, needed to enhance photostability, efficacy, or safety of the active ingredient to establish its GRASE status.

III. SAFETY DATA NEEDED TO ESTABLISH THAT AN OTC SUNSCREEN ACTIVE INGREDIENT IS GRASE

FDA’s OTC drug regulations identify the general types of safety information that sponsors should submit as evidence that an OTC drug is GRASE for use as labeled (21 CFR 330.10(a)(2)) and the standard by which safety is to be judged (21 CFR 330.10(a)(4)(i)). When applying these regulations to each potential active ingredient, FDA uses its scientific expertise to determine

¹¹ For example, if key studies were conducted using a related but different compound, or using a combination of active ingredients whose individual contributions to the observed results were not examined, those studies may have little relevance to a GRASE determination for the sunscreen active ingredient identified by the requested quality/manufacturing data.

¹² The determination of whether a sunscreen active ingredient is GRASE and not misbranded also requires the Agency to describe the conditions under which any future product incorporating that sunscreen active ingredient will be GRASE and not misbranded. See, for example, section 586C(e) of the FD&C Act. For further discussion see section V.

Contains Nonbinding Recommendations
Draft — Not for Implementation

what constitutes “adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use.”¹³

In the case of OTC sunscreen active ingredients, FDA balances the important role that broad spectrum sunscreens with a sun protection factor (SPF) value of 15 or higher play in decreasing the risk of skin cancer and early skin aging caused by the sun, if used as directed with other sun protection measures; the benefits, with the public health importance of providing an adequate safety margin¹⁴ for OTC sunscreen active ingredients and finished sunscreen products, versus the risks. When determining the specific testing and other data needed to adequately demonstrate that an OTC sunscreen active ingredient is safe, FDA considers both the circumstances under which OTC sunscreen products are intended to be used by consumers and current scientific knowledge and assessment technology.

To ensure full discussion of the kinds of data needed to address sunscreen safety, FDA held a 2-day meeting of the Nonprescription Drugs Advisory Committee on September 4-5, 2014, at which FDA presented much of the same approach that is recommended in this guidance. There was consensus among the independent scientific experts on the committee that FDA’s framework was a good starting point.¹⁵ This guidance takes into consideration the recommendations FDA received from this committee.

FDA’s current approach to clinical safety evaluation of potential OTC sunscreen active ingredients is based on current scientific understanding regarding safety evaluation of topical products for chronic use, and thus is generally consistent with the safety data requirements that would apply to an NDA for a chronic-use cutaneous drug product (i.e., topical safety studies (irritation, sensitization, and photosafety), bioavailability (absorption), and evaluation of adverse events observed in clinical studies).¹⁶ In addition, the evaluation of adverse events reported during the commercial marketing of sunscreen products containing the ingredient and other postmarketing safety information is also relevant to safety.

FDA’s current approach to the nonclinical safety evaluation of these active ingredients takes into account that only active ingredients that have been marketed to a material extent and for a material time in OTC sunscreen products are eligible under the SIA for a GRASE determination and inclusion in the OTC sunscreen drug monograph.¹⁷ In contrast to nonclinical data requirements for a chronic-use cutaneous drug product NDA, which include comprehensive

¹³ 21 CFR 330.10(a)(4)(i)

¹⁴ A *safety margin* is an estimated exposure level in humans that is calculated based on toxic effects seen in animal studies; the safety margin is used to predict a safe exposure level in humans well below where toxicities were seen in animals.

¹⁵ See the minutes of the FDA September 4-5, 2014, meeting of the Nonprescription Drugs Advisory Committee (2014 NDAC Minutes) at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm380890.htm> (accessed October 8, 2015).

¹⁶ *Chronic use* is defined as continuous or intermittent use for at least 6 months during the course of a lifetime.

¹⁷ See section 586B(a)(2) of the FD&C Act.

Contains Nonbinding Recommendations
Draft — Not for Implementation

nonclinical pharmacology and toxicology safety testing, the approach to nonclinical safety testing in this guidance is largely focused on potential long-term adverse effects or effects not otherwise readily detected from human use (i.e., carcinogenicity and reproductive toxicity). Additional testing beyond what is recommended in this guidance may be needed for active ingredients for which data suggest a concern about other long-term effects, such as hormonal disruption.

The following sections describe the specific safety data that FDA needs to determine whether an active ingredient is GRASE for use in sunscreens. However, FDA will consider alternative scientifically based approaches for addressing a particular data need. Sponsors are encouraged to discuss alternative proposals with FDA before initiating studies.

A. Clinical Safety Testing

1. Human Dermal Safety Studies

Human dermal safety studies for topical products in which exposure to light after application is anticipated generally consist of two sets of studies — those conducted without specific exposure to light and those conducted to assess reactions after ultraviolet exposure (photosafety studies).¹⁸ The studies usually consist of dermal irritation patch testing, dermal sensitization patch testing, dermal phototoxicity testing, and dermal photoallergenicity testing.

Because marketed sunscreen products typically contain a combination of active ingredients, and brand name product formulations frequently change, it is difficult to determine causal links between individual active ingredients and reported irritation and hypersensitivity adverse events associated with a particular product. Therefore, FDA generally expects to use data from human irritation studies, human skin sensitization studies, and human photosafety studies, in conjunction with postmarketing adverse event data, to inform GRASE determinations and labeling. Nonetheless, in some cases, it may be reasonable to omit human irritation studies, human skin sensitization studies, and/or human photosafety studies, depending on the rigor of available postmarketing safety information. For example, if FDA concludes that there is a positive risk-benefit for a sunscreen active ingredient but that it is known to be a sensitizer, it may be possible to develop safety labeling to address this risk without data generated in the human dermal safety studies described below. Sponsors who believe there is a scientific rationale that may preclude the need for some or all of the described studies are urged to contact FDA before initiating studies.

a. Human irritation and sensitization studies

Studies of skin irritation and sensitization, using the repeat insult patch test or other relevant tests, are recommended elements in the safety evaluation of topical drug products that, like sunscreens, are applied to the skin repeatedly over long periods of time. Designed to detect the potential for local dermatologic events with fewer subjects than might be observed in larger

¹⁸ See the ICH guidance for industry *S10 Photosafety Evaluation of Pharmaceuticals*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations
Draft — Not for Implementation

clinical trials, these tests often employ product application that can be more frequent and/or for longer duration than proposed clinical dosing. In dermal irritation studies, a test substance is applied to a small pad (patch) and affixed to the test subject's skin, usually on the back, to determine whether the ingredient causes direct skin toxicity. Dermal sensitization studies are conducted similarly, but are designed to detect immunologically mediated reactions, which require prior exposure to the allergen.

Nonprescription sunscreen active ingredients, when found GRASE, may be used in numerous, as yet unknown, product formulations. Therefore, FDA recommends that cumulative irritation studies evaluate the proposed sunscreen active ingredient at the highest concentration for which a GRASE determination is sought, in an appropriate vehicle, the vehicle alone, and with both negative and positive controls. The evaluation should include scoring of erythema, edema, and a papular response or skin erosion.

Skin sensitization studies, conducted to detect immunologically mediated reactions, should be conducted in three phases:

- (1) The induction phase (three weekly applications for 3 weeks)
- (2) The rest phase (no product application for 10 to 14 days)
- (3) The challenge phase (patch applications to new sites for 48 hours with a confirmatory rechallenge to exclude false positives)

Although FDA recommends separate dermal irritation and sensitization studies, irritation and sensitization studies can be combined in the same study as long as a sufficient number of subjects are included for sensitization evaluation.

b. Human photosafety studies

Topically applied dermatologic drug products should be tested for photosafety if they absorb light in the ultraviolet A (UVA), ultraviolet B (UVB), or visible spectra. FDA recommends that photosafety evaluations of sunscreen active ingredients that absorb light consist of skin photoallergenicity and skin phototoxicity testing. Photoallergy is an immunologically mediated reaction to a chemical, initiated by the formation of photoproducts (e.g., protein adducts) following a photochemical reaction. As does dermal sensitivity testing described above, these tests use an induction/rest/challenge/rechallenge multiphase design to assess erythema, edema, and vesiculation. Phototoxicity (photoirritation) is an acute light-induced tissue response to a photoreactive chemical. Testing typically includes a test patch, a vehicle patch, and a sham patch application for 24 hours, followed by ultraviolet light exposure of the test area. A second set of patch application areas not irradiated with light serves as a control. FDA recommends that photosafety studies of sunscreen active ingredients that absorb light be conducted using the active ingredient at the highest concentration for which a GRASE determination is sought in an appropriate vehicle, the vehicle alone, and a negative control.

Contains Nonbinding Recommendations
Draft — Not for Implementation

2. *Human Absorption Studies/Maximal Usage Trial*

Because nonprescription sunscreens are topically applied, a critical safety consideration is whether dermal application results in skin penetration and systemic exposure to the active ingredient and, if so, to what extent. This information helps identify potential safety concerns and helps determine whether an adequate safety margin exists for an active sunscreen ingredient to be included in the OTC sunscreen monograph.

The principal barrier to cutaneous drug product penetration is the multilayered, lipid-rich stratum corneum. The passage of any drug product through this layer is influenced by many factors, including the drug product's physicochemical features, molecular weight, and vehicle/formulation properties. Vehicle/formulation properties are particularly important because the choice of vehicle can markedly affect the permeation potential of a drug product. Effects can range from simple hydration of the stratum corneum by occlusive vehicles/formulations to direct permeation enhancement by solvent effects on the lipids in the stratum corneum. Products absorbed through the skin have the potential to cause systemic adverse effects, affecting the safety assessment. Because sunscreens are intended to work at the skin's surface, systemic absorption may also lower efficacy, affecting the efficacy assessment.

Since the mid-1990s, topical product NDAs have included a Maximal Usage Trial (MUsT) as part of the clinical pharmacology/bioavailability assessment. A MUsT is designed to capture the effect of *maximal use* on absorption into the blood with standard pharmacokinetic assessments (e.g., C_{\max} , T_{\max} , area under the curve, half-life, clearance, and volume of distribution). For an NDA, the MUsT is conducted in subjects with the disease of interest and with the specific product formulation for which approval is sought applied at the upper limit of surface area involvement that is studied in the phase 3 clinical trials and is proposed for labeling. That is to say, if the proposed labeling permits the product to be used on up to 30 percent of body surface area, that would be the coverage evaluated in the MUsT.^{19,20}

FDA recommends that sponsors of sunscreen active ingredients provide data from a MUsT to support an adequate assessment of safety.²¹ Because a determination that an active sunscreen product is GRASE would permit its use in a variety of finished sunscreen products, FDA recommends that the MUsT be conducted under maximal use conditions employing a minimum of four formulations containing the new sunscreen active ingredient as the only active ingredient to support the GRASE determination. These formulations should be prepared using vehicle/formulation systems that are appropriate for sunscreen topical products (e.g., deployability, spreadability) and that are expected to produce the highest in vivo absorption. Justification for the formulations chosen, including results of in vitro testing using a human

¹⁹ Bashaw ED, Tran DC, Shukla CG, et al., 2014, Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products, Therapeutic Innovation & Regulatory Science, published online 27 June 2014, DOI:10.1177/2168479014539157.

²⁰ See the draft guidance for industry *Acne Vulgaris: Developing Drugs for Treatment*. When final, this guidance will represent the FDA's current thinking on this topic.

²¹ See 2014 NDAC Minutes, *supra* note 15 at 6 (response to Discussion Question 1) (expressing need for human maximal use studies in all cases).

Contains Nonbinding Recommendations
Draft — Not for Implementation

cadaver skin permeation system (e.g., static or flow-through cells),²² should be included in the study protocol. The protocol should contain sufficient detail for others to reproduce the formulations and manufacturing process.

FDA anticipates that the use of multiple formulations will help identify the overall absorption potential of the sunscreen active ingredient of interest. The MUsT should be conducted in subjects with normal (nondiseased) skin at the highest concentration of the ingredient for which a GRASE determination is sought and eligibility under the SIA has been established. Based on recommended sunscreen use on all exposed skin, the exposed area should include nearly all of the body surface area. Data from the formulation that produces the highest in vivo absorption would then be used to determine the safety margin.

The assay used in the MUsT should be properly validated according to current good laboratory practices (21 CFR part 58) and should be consistent with the guidance for industry *Bioanalytical Method Validation*. The assay's limit of quantitation-limit of detection should be sufficiently low to allow a signal:noise ratio that ensures confidence in detection of a derived concentration of 0.5 nanogram (ng)/milliliter (mL).

An important consideration for designing a MUsT is that it includes testing for a duration that allows for the attainment of steady state levels to ensure that maximum penetration of the ingredient has taken place and to optimize its chances of being detected. Thus, for sunscreen ingredients, FDA expects that single application studies would be inadequate. Because the subjects in a MUsT represent an enriched dataset in the upper range of exposures, FDA currently recommends collection of safety-related data (such as vital signs, adverse skin events) from the study's regularly scheduled physical examinations. Sponsors are strongly encouraged to discuss their MUsT protocol with FDA before beginning the trial. As discussed further in section V, if the sunscreen active ingredient is determined to be GRASE, FDA believes that it would be appropriate to designate the formulation that produces the highest in vivo absorption in the MUsT as a standard control formulation for future in vitro human cadaver skin permeation system testing (e.g., static or flow-through cells) of each final sunscreen formulation that includes that active ingredient.

If in vitro permeation of the sunscreen active ingredient in the final product formulation is equal to or less than the value from in vitro testing of the standard control formulation (that was shown by the MUsT to have the highest degree of systemic absorption), FDA anticipates that the safety margin calculated would be considered adequate to support the finished formulation.

3. Pediatric Considerations

Young children have a larger ratio of skin surface to body volume compared to adults, which can increase a child's systemic exposure to topically applied drug products. In addition, growing children have greater potential to experience deleterious developmental effects from drug exposure. If the calculated safety margin for a proposed monograph active ingredient (based on nonclinical results and human MUsT) supports a GRASE determination but the safety margin is

²² Bronaugh R and Stewart F, 1985, Methods for In Vitro Percutaneous Absorption Studies IV: The Flow-Through Diffusion Cell, J. Pharm. Sci, 74(1), 64-67.

Contains Nonbinding Recommendations
Draft — Not for Implementation

relatively small, FDA will exercise its scientific judgment to determine if a sunscreen active ingredient MUSt in young children or other studies are warranted to ensure that the safety margin for marketed products containing the ingredient is within an acceptable range for this population.

B. Nonclinical Safety Testing

1. Carcinogenicity Studies: Dermal and Systemic

FDA generally recommends carcinogenicity studies for any pharmaceutical with an expected continuous clinical use of at least 6 months or when used for a minimum of 6 months in an intermittent manner.²³ The animal carcinogenicity studies help characterize the potential tumor risks associated with a sunscreen active ingredient by identifying any observed tumors by type, the level of exposure at which tumors occur, and the highest level of exposure at which no adverse effects occur, referred to as the *no observed adverse effect level (NOAEL)*. The NOAEL would be used in determining the safety margin for human exposure to sunscreens containing the active ingredient. In addition to detecting carcinogenic potential, carcinogenicity studies in animals can also help to identify other systemic or organ toxicities that may be associated with the proposed ingredient.

A dermal carcinogenicity study that involves applying the product to the skin of mice or rats for 2 years is thus recommended to support OTC sunscreen active ingredients. FDA also considers it important to study the effects of systemic exposure if human bioavailability data show that dermal application of a particular formulation could potentially result in skin penetration and systemic exposure. After the active ingredient is marketed in nonprescription sunscreens, that active ingredient is likely to be used in a wide variety of product formulations that might alter its skin penetration. Therefore, a second carcinogenicity study by a route that produces systemic exposure is also generally recommended. This can be a 2-year study or a shorter (usually 6 months) alternative carcinogenicity model and should be conducted in a species different from that used in the dermal carcinogenicity study. All carcinogenicity studies regardless of route should assess a full panel of tissues.²⁴

2. Developmental and Reproductive Toxicity Studies

Developmental and reproductive toxicity (DART) studies are recommended to evaluate the potential effects that exposure to the sunscreen active ingredient may have on developing offspring throughout gestation and postnatally until sexual maturation, as well as on the

²³ See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*.

²⁴ FDA expects that a systemic carcinogenicity study would not be needed to support a GRASE determination for a sunscreen active ingredient if an adequately conducted human pharmacokinetic MUSt results in a steady state blood level less than 0.5 ng/mL and an adequately conducted toxicology program does not reveal any other safety signals for the ingredient or any known structurally similar compound indicating the potential for adverse effects at lower levels. The threshold value of 0.5 ng/mL is based on the principle that the level would approximate the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100,000 after a single dose.

Contains Nonbinding Recommendations
Draft — Not for Implementation

reproductive competence of sexually mature male and female animals.²⁵ Gestational and neonatal stages of development may be particularly sensitive to active ingredients with hormonal activity (endocrine disruption). For this reason, FDA recommends that these studies include assessments of endpoints such as vaginal patency, preputial separation, anogenital distance, and nipple retention, which can be incorporated into traditional DART study designs to assess potential hormonal effects on the developing offspring. FDA also recommends performing behavioral assessments (e.g., mating behavior) of offspring, which may detect neuroendocrine effects.²⁶

3. *Toxicokinetics*²⁷

FDA recommends collecting animal toxicokinetic data for sunscreen active ingredients because these data provide an important bridge between toxic levels seen in animal studies and any potential human adverse events associated with systemic exposure to the sunscreen's active ingredient (see section III.A.2). Toxicokinetic measurements usually are obtained during the course of ongoing nonclinical toxicity studies, such as carcinogenicity or DART studies, rather than through separate studies.

C. Postmarketing Safety Data

In addition to the active ingredient safety data already described, FDA's GRASE evaluation also takes into consideration available information about serious adverse drug experiences and known or expected adverse effects associated with commercially marketed products that contain the active ingredient(s) under consideration. FDA specifically requests the following information:

- A summary of all potentially associated serious adverse drug experiences.
- A summary of all available potentially associated nonserious adverse drug experiences.
- A summary of expected or frequently reported side effects, whether serious or nonserious.
- Copies of all available reports of potentially associated serious adverse drug experiences, in the form of individual case safety reports as described in 21 CFR 314.80. Each report submitted should refer only to an individual consumer or a single attached publication.

²⁵ See the ICH guidance for industry *S5A Detection of Toxicity to Reproduction for Medicinal Products*. FDA expects that studies to assess fertility and pre- or postnatal toxicity may not be needed if an adequately conducted human MUsT shows absorption that results in a steady state blood level less than 0.5 ng/mL, and there are no signals in an adequately conducted toxicology program indicating the ingredient or any known structurally similar compound interacts with related pathways, such as endocrine function or signaling pathways related to growth and development.

²⁶ See the guidance for industry *Nonclinical Evaluation of Endocrine-Related Drug Toxicity*.

²⁷ See the ICH guidance for industry *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.

Contains Nonbinding Recommendations
Draft — Not for Implementation

- Any available safety information from studies of safety and effectiveness in humans.
- Relevant medical literature describing associated adverse events.

English translations should be provided for all foreign language materials.

For products marketed outside the United States, submissions should also state whether each country's system allows for adverse event reporting and, if so, how each country's system identifies and collects the adverse events.²⁸ If adverse event information is not available from all countries where the active ingredient has been marketed in OTC sunscreen products, the sponsor should provide an explanation for the missing data. It is important to note, however, that even when countries have an adverse event reporting system that includes sunscreen products, underreporting is a significant limitation of any system that depends on spontaneous reports.

Many factors can influence whether an adverse event is reported, including whether a possible relationship between the event and an ingredient or product is recognized by consumers or health care providers. For example, adverse events that occur many years after a causal drug exposure may not be recognized as such, especially if the background rate of the event is high (e.g., a common cancer or developmental problem). Thus, absence of reports does not necessarily equate to absence of adverse events. Despite the limitations of adverse event reporting, FDA considers postmarketing data to be relevant both to the overall GRASE assessment of OTC sunscreen active ingredients and to labeling considerations because these data may reveal safety signals not otherwise observed in clinical or nonclinical testing.

IV. EFFECTIVENESS TESTING

FDA's OTC drug regulations generally identify the types of effectiveness information that sponsors should submit as evidence that a drug product containing an active ingredient or other OTC drug condition could be GRASE for use as labeled (21 CFR 330.10(a)(2)) and the standard by which effectiveness is to be judged, which requires controlled clinical investigations to support effectiveness (21 CFR 330.10(a)(4)(ii)).

When applying these regulations to each potential sunscreen active ingredient, FDA requests evidence from at least two adequate and well-controlled SPF studies showing that the active ingredient effectively prevents sunburn, because sunburn prevention is the minimum indication for an OTC sunscreen product. Two adequate and well-controlled SPF studies of the active ingredient at a lower concentration than the maximum requested should be conducted according to established standards.²⁹ These SPF studies should demonstrate that the selected concentration provides an SPF value of 2 or higher.

²⁸ See, for example, 21 CFR 330.14(c)(2)(v).

²⁹ FDA expects that the upper bound of any concentration of the active ingredient ultimately established would be governed by the safety data, as well as by efficacy.

Contains Nonbinding Recommendations
Draft — Not for Implementation

The current standard procedure for SPF testing is described in 21 CFR 201.327(i).³⁰ Any new SPF tests for a particular ingredient should be performed as described in these regulations, using a test formulation containing the ingredient as the only active ingredient to identify its contribution to the overall SPF test results. The study should also include a vehicle control arm to rule out any contribution the vehicle may have on the SPF test results. Finally, as described in 21 CFR 201.327(i), an SPF standard formulation comparator arm should be another component of the study design.

Current sunscreen testing and labeling regulations in 21 CFR 201.327(j) also specify a broad spectrum testing procedure, which provides an in vitro measurement of a sunscreen product's ability to protect against both UVA and UVB radiation. Although this test can be used to support related labeling claims for sunscreen products marketed under the stayed final monograph, those additional claims are permitted, but not required.³¹ Broad spectrum protection is often the result of the combined contribution of multiple active ingredients in a final sunscreen formulation. Thus, FDA does not expect that a sunscreen active *ingredient* would undergo broad spectrum effectiveness testing to establish its effectiveness for a GRASE determination for use in OTC sunscreen products.

Under 21 CFR 201.327, the determination of whether an individual sunscreen product subject to that rule may be labeled as broad spectrum and bear the related additional claims is made on a product-specific basis, applying the standard testing methods set forth in those regulations. These test procedures are also described in the guidance for industry *Labeling and Effectiveness Testing: Sunscreen Drug Products for Over-The-Counter Human Use — Small Entity Compliance Guide*. If a sunscreen active ingredient evaluated under the SIA is established to be GRASE for use in nonprescription sunscreens, the final sunscreen order can likewise address broad spectrum testing and related labeling conditions for final sunscreen formulations containing that ingredient.

V. ANTICIPATED FINAL FORMULATION TESTING

Preceding sections of this guidance concentrate on recommendations for safety and effectiveness data needed to support FDA's determination that a sunscreen active ingredient is GRASE for use in sunscreens. FDA's determination that an active ingredient is GRASE will be made in the form of a final sunscreen order that will set out the conditions under which any future product incorporating that sunscreen active ingredient will be GRASE and not misbranded (see section

³⁰ Although the SPF testing procedure is used primarily for final formulation testing of finished products marketed without approved NDAs, it is equally applicable for determining whether or not a sunscreen active ingredient is generally recognized as effective as part of the overall GRASE determination.

³¹ FDA strongly encourages manufacturers to develop OTC sunscreen products that provide broad spectrum protection and have an SPF value of 15 or higher because of the deleterious health effects that may result if consumers increase their overall sun exposure through use of sunscreen products that help prevent sunburn, but do not provide sufficient protection to help reduce the risk of skin cancer and early skin aging caused by the sun. FDA requires these *sunburn only* products to bear a prominent warning stating: “**Skin Cancer/Skin Aging Alert:** Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, **not** skin cancer or early skin aging” (21 CFR 201.327(d)(2)).

Contains Nonbinding Recommendations
Draft — Not for Implementation

I).³² As noted in section III.A.2, variations among individual sunscreen products — and in particular, aspects of the lotion or other vehicle in which active ingredients are delivered — can affect absorption and thus safety and effectiveness.

To address this variability among sunscreen formulations containing the same active ingredient(s), FDA requires final formulation testing of nonprescription sunscreen products to ensure their *effectiveness* — namely testing for SPF value as well as broad spectrum protection and water resistance, where those attributes are claimed in product labels.³³ Likewise, FDA anticipates that final sunscreen orders issued for sunscreen active ingredients determined to be GRASE under the SIA would include conditions requiring final formulation testing to ensure the *safety* of all sunscreen formulations permitted by the order.

The discussion that follows provides FDA’s current thinking about such final formulation safety testing, to be conducted in the future. The public is encouraged to comment on this general approach when commenting on this draft guidance. Note that FDA has not yet determined whether final formulation testing as described in this draft guidance will be a necessary condition for determining whether each of the individual sunscreen active ingredients is GRASE for use alone or in combination in a sunscreen product. Making that determination for a specific ingredient requires consideration of the data recommended to be supplied under other parts of this guidance to support a GRASE determination (e.g., whether any safety signals are detected in well-conducted nonclinical carcinogenicity and DART studies). Interested parties also can provide relevant information and comment for an individual sunscreen active ingredient as part of the process for GRASE determination for that ingredient. FDA is particularly interested in comments that include a scientifically persuasive rationale as to why it is not necessary to conduct the anticipated final formulation safety testing for a particular sunscreen active ingredient, or that provide an alternative, scientifically supported approach to ensure that formulated sunscreen products containing that ingredient will have an acceptable safety margin.

Specifically, FDA’s current thinking is that final formulation safety testing of nonprescription sunscreens would not generally call for in vivo study. Instead, FDA expects that the conditions of marketing for sunscreen active ingredients would require manufacturers to perform in vitro permeation testing before marketing each new formulation as described in the following paragraphs.³⁴ Consistent with the approach for final formulation efficacy testing required by 21 CFR 201.327, FDA would not review the results of the in vitro final formulation safety testing before product marketing. Rather, FDA expects that the conditions of marketing for sunscreen active ingredients described in final sunscreen orders would require manufacturers to maintain records of this testing. These records would be available to FDA.

³² See section 586D(e) of the FD&C Act.

³³ See 21 CFR 201.327 for the current requirements for OTC sunscreens containing the active ingredients already evaluated under the monograph system. OTC sunscreens marketed under NDAs provide similar information in their product-specific applications to substantiate their labeling.

³⁴ FDA recommends this approach as an alternative to final in vivo (MUsT) testing of final product formulations, which was recommended by the Nonprescription Drugs Advisory Committee. See 2014 NDAC Minutes, *supra* note 15 at 7 (Discussion Question 2).

Contains Nonbinding Recommendations
Draft — Not for Implementation

First, as mentioned in section III.A.2, FDA anticipates establishing a standard control formulation for each sunscreen active ingredient, to be used in this final formulation testing of products containing that ingredient. The standard control formulation would be the formulation that produces the highest in vivo absorption in the MUSt. The results of in vitro human cadaver skin testing using this control formulation can then be used to bridge to a corresponding level of in vivo absorption from the MUSt used to establish the safety margin for the GRASE ingredient.

Then, FDA anticipates that final formulation testing would be conducted for each formulation intended to be marketed, by testing both the new formulation and the standard control formulation, using the same type of human cadaver skin diffusion cell: Franz (static) or Bronaugh (flow-through). The results of the in vitro permeation testing of the new formulation would then be compared to the values determined for the standard control formulation for the active ingredient it contains. If a final sunscreen formulation contains multiple sunscreen active ingredients, FDA anticipates that the final formulation would be tested against the standard control formulations for each of the sunscreen active ingredients it contains.

If in vitro permeation of each sunscreen active ingredient in the final formulated product is equal to or less than the value obtained from in vitro testing of the standard control formulation for that active ingredient, FDA anticipates that the product's safety margin would be considered to fall within the parameters judged to be GRASE and thus to support marketing of the new formulation. However, if the in vitro permeation of the active ingredient from the specific final formulation is greater than the value obtained from in vitro permeation testing of the standard control formulation for that active ingredient, the formulation would not be considered GRASE.

If the results of the testing show that in vitro permeation of the sunscreen active ingredient in the final formulated product is greater than the value obtained from testing of the standard control formulation for that active ingredient, manufacturers would have the following options:

- Reformulate the product and repeat the in vitro testing
- In particular cases where the difference in permeation is small, consult with FDA as to whether the new formulation's safety margin may be considered acceptable
- Conduct a MUSt evaluation of the final formulation itself using the recommendations described in section III.A.2 to establish an acceptable safety margin for the final formulation
- Seek NDA approval for the new formulation